

# Cytologic Diagnosis of Gastric Cancer

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■ *Follow-up of cytologic examinations of specimens obtained from 187 patients by gastric lavage with saline solution, without the use of enzymes or abrasive devices, showed a false positive rate of 0.6 per cent and a false negative rate of 17 per cent.*

*To achieve satisfactory results with such examinations, great attention to detail in obtaining, preparing and examining the specimens is essential. Cytologic examination should be done in any case in which gastric cancer is suspected clinically or roentgenographic or gastroscopic findings arouse suspicion.*

EXFOLIATIVE CYTOLOGY is very useful in the diagnosis of carcinoma of the stomach. The clinical diagnosis of early gastric carcinoma is notoriously inaccurate. Radiologic study of the stomach, although 90 to 95 per cent accurate in detecting the presence of a gastric lesion, is only 70 to 80 per cent accurate in distinguishing whether the lesion is benign or malignant.<sup>3,5,8,12</sup> It is even less accurate in the detection of superficial spreading carcinoma of the stomach. Gastroscopy has comparable limitations in accuracy, besides being uncomfortable for the patient and technically difficult.<sup>3,5</sup> Exfoliative cytology has been shown by several investigators<sup>3,5,11</sup> to be more accurate than roentgenography or gastroscopy in determining whether a gastric lesion is malignant, and it is simple enough to be performed in any pathology laboratory that has well trained cytotechnologists.

The cytologic diagnosis of gastric carcinoma was first reported by Beale<sup>1</sup> in 1858 after he had examined unstained smears of vomitus for malignant cells. Marini<sup>7</sup>, who in 1909 was the first to

use gastric lavage for obtaining the specimens, detected malignant cells on unstained smears of aspirate in 32 of 37 cases of gastric carcinoma. The first report of the staining of smears of gastric aspirate for cytologic examination was made by Loeper and Binet<sup>4</sup> in 1911. After a 30-year hiatus, a great resurgence of interest followed the work of Papanicolaou who in the 1940s extended his studies on gynecologic exfoliative cytology to the stomach and other anatomic sites.<sup>10</sup> During the past decade, several series have been recorded which demonstrate the accuracy of the procedure (see Table 1).

## Present Series

Gastric lavage with saline solution to obtain specimens for cytologic examination (a technique previously described by other investigators<sup>9,10,11</sup>) has been used for more than six years at the Hospital of the Good Samaritan Medical Center, Los Angeles. It has proved most useful in determining whether cancer is or is not present in suspected cases. The technique is relatively simple, and the accuracy of results is comparable with that achieved when more complex aspiration procedures are used to obtain gastric cells for cytologic

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**TABLE 1.—Review of Literature Relative to Accuracy of Exfoliative Gastric Cytology in Diagnosis of Cancer**

Date	Reported by (Reference)	Total Number of Cases	False Negatives (Proved Gastric Cancer)			False Positives (Proved or Apparently Benign)		
			Cases	False	Per Cent False	Cases	False	Per Cent False
1960	Schade (9)	558	282	6	2	276	13	5.0
1962	Von Haam (13)	1,050	50	7	14	1,000	14	1.4
1963	MacDonald (5)	380	89	6	7	291	1	0.3
1964	Yamada (14)	337	181	34	19	156	5	3.0
1964	Henning (3)	380	227	39	17	153	6	4.0
1965	Taebel (11)	1,866	282	53	19	1,584	4	0.25
1967	Present report	184	29	5	17	155	1	0.6

study. In one of the more elaborate methods, the proteolytic enzyme chymotrypsin, which is said to increase the yield of exfoliated cells by dissolving the coat of mucus over the gastric mucosa, is added to the lavage solution.<sup>5,6,14</sup> Other investigators advocate the use of various abrasive devices or sponges<sup>3</sup> to cause exfoliation of mucosal cells. These techniques are not only more complex but they cause the patient discomfort and they entail some risk. We have found the saline lavage to be simple, free of discomfort and complications, and productive of well preserved exfoliated cells in adequate number.

## Technique

The entire aspiration procedure is performed by cytotechnologists or nurses trained and supervised by physicians in the Department of Pathology. (Random specimens obtained by untrained nurses or other untrained personnel are generally useless, for usually they contain few exfoliated cells and even those present are badly degenerated.)

The evening before the specimen is to be obtained, the patient is permitted to have only a light liquid meal. To assure adequate hydration, he must drink several glasses of water at bedtime and on arising. He cannot have breakfast. A No. 18 rubber Levin tube, not lubricated, is passed through the mouth into the stomach to the 55 or 60 cm mark. The gastric residual fluid is then aspirated, checked for free acid, and discarded. A 50 ml catheter irrigation syringe with a large orifice is used to

wash the stomach twice with 300 to 500 ml of normal saline solution. Each time the solution is repeatedly and vigorously injected, aspirated, reinjected and reaspirated. The first lavage serves to remove the mucous coat and the aspirated liquid is discarded; the material aspirated after the second lavage is saved for cytologic examination. During lavage the patient changes position, from prone to supine to one side and then the other, and the abdomen is massaged while he is supine. Also, the position of the tube is moved frequently to assure irrigation of large areas of gastric mucosa.

The aspirate from the second lavage is immediately placed in glass specimen bottles which are already immersed in ice. The specimens are kept in ice and are immediately returned to the laboratory for processing. Speed is essential and is the key to accurate interpretation, since gastric enzymes and acid rapidly destroy the cells. The aspirate is centrifuged on a table top centrifuge at high speed for 5 minutes in 40 ml cylindrical glass centrifuge tubes. The supernatant is decanted and a spatula is used to smear the sediment on clear glass slides previously coated with a thin layer of albumin. Four slides are prepared for each case. The slides are fixed in Carnoy's medium\* for a half hour to two days. This causes lysis of any erythrocytes that may be present. The smears are stained with regular Papanicolaou stain and are screened by trained cytotechnologists. Final interpretation is made by a pathologist. It should be

\*Carnoy's medium is prepared by mixing 70 ml of 95 per cent ethanol, 25 ml of chloroform, and 5 ml of glacial acetic acid.

**TABLE 2.—Follow-up of Gastric Cytologic Examinations**

Cytologic Diagnosis		Total Number of Cases	Proved or Apparently Benign	Proved Malignant	No Follow-up
Negative—	Class I—Normal and				
	Class II—Atypical	158	153	5	0
Suspicious—	Class III	5	1	2	2
Positive—	Class IV—Very Suspicious and				
	Class V—Malignant	24	1	22	1

TABLE 3.—Accuracy of Gastric Cytologic Examination

Final Diagnosis	Total Number of Cases	False Negative	False Positive
Proved or Apparently Benign	155		1 of 155 (0.6%)
Proved Malignant	29	5 of 29 (17%)	...

noted that if both cytologic examination and timed gastric analysis for acid are desired, the lavage for cytologic specimens is performed first.

## Results

In a period of five and a half years between January 1961 and June 1966, 187 inpatients at The Hospital of the Good Samaritan Medical Center had gastric cytologic examinations. Follow-up was obtained on 184. Of 155 patients who ultimately were proved not to have gastric cancer only one had a cytologic test interpreted as positive, a false positive rate of 0.6 per cent. In that one case the interpretation was Papanicolaou Class IV (very suspicious of cancer). In none of the cases in which the interpretation was Class V (diagnostic for malignant disease) did the patient prove not to have cancer. Of the 29 cases in which malignant disease was later proved, five were missed cytologically, the slides being interpreted as Class I or Class II. Thus the false negative rate was 17 per cent. Four of the 29 patients with malignant disease had malignant lymphomas and the remaining 25 had adenocarcinomas. Of the 24 cases with positive cytologic diagnosis (Class IV and Class V), ten were of Class IV and 14 Class V. Of the 24 patients with diagnosis of "positive" by cytologic examination, 22 proved to have cancer, one was proved not to have the disease and adequate follow-up was not available on the remaining case. In only five of the 187 cases was the slide read as Class III (suspicious); we attempt to hold the number of Class III reports to a minimum as this classification is least helpful to the clinician.

There are situations in which cytologic examination of material obtained by gastric lavage are of particular value, as in the following cases:

CASE 1.—A 61-year-old white woman was well until the sudden onset of gastrointestinal bleeding. X-ray studies showed a 2.5 cm ulcerated lesion on the lesser curvature of the stomach. The radiologist was unable to determine whether it was benign or malignant. Gastric cytologic examination was positive (Class V), with cells characteristic of adenocarcinoma (Figures 1 and 2). Radical total gastrectomy was performed. The lesion was an



Figure 1.—(Case 1) Adenocarcinoma  $\times 1,000$ .

ulcerating adenocarcinoma with metastasis to lymph nodes along the lesser curvature.

*Comment:* The ulcerated gastric lesion was detected radiologically but, as frequently happens, a decision could not be made as to whether it was a benign peptic ulcer or an ulcerated adenocarcinoma. A definitive diagnosis of malignant disease was made cytologically. Having a definitive diagnosis, the surgeon was able to proceed directly with a radical total gastrectomy without the necessity of first opening the stomach and taking a specimen of the lesion for frozen section.

CASE 2.—A 63-year-old white woman first had had gastric ulcer on the lesser curvature, diagnosed



Figure 2.—(Case 1) Adenocarcinoma  $\times 1,000$ .

radiologically, in 1957. It completely healed on conservative therapy. In 1961, after recurrence of epigastric pain, x-ray studies were normal and gastroscopy was unsuccessful; gastric cytologic study then was negative (Class II). Conservative therapy was again successful until early in 1963, when symptoms recurred. X-ray studies revealed redundant mucosa high on the lesser curvature, and gastric cytologic smears were again interpreted as Class II, with atypical cells present but no malignant cells identified. In March 1963, at gastrotomy, a large circumferential juxta-esophageal gastric ulcer was found. Biopsy of the lesion showed only atypical epithelial hyperplasia, and distal gastrectomy and vagotomy were performed. X-ray studies later showed healing of the ulcer, but dysphagia persisted. In December of 1963, repeat cytologic examination showed malignant cells characteristic of adenocarcinoma (Class V). Surgical resection of the proximal stomach was then done and it contained a superficial spreading carcinoma arising in the margins of a chronic peptic ulcer of the cardia. There was a single minute metastatic focus in one gastric lymph node. Laparotomy in November 1965 to relieve intestinal obstruction showed peritoneal carcinomatosis, proved by biopsy. The patient died in May 1966.

*Comment:* The long history of benign gastric ulcer, documented by x-ray studies and biopsy, was followed six years later by the development of a superficial spreading adenocarcinoma of the stomach, which was detected only by positive gastric cytologic examination. Schade<sup>9</sup> described 16 cases of superficial spreading or surface carcinoma, and he expressed belief that in all such cases there is accompanying chronic gastritis. Carcinoma of this type may sometimes be diagnosed cytologically in an early curable stage, before it is radiologically or gastroscopically detectable. Unfortunately in this case metastasis had already occurred.

**CASE 3.**—A 75-year-old white man had a two-month history of epigastric pain. X-ray films revealed a defect on the greater curvature, felt to be an early carcinoma. Gastric cytologic examination (Figure 3) revealed cells very suspicious for malignant change (Class IV). At operation a mass was found along the greater curvature with grossly enlarged lymph nodes. Biopsy showed a reticulum-cell sarcoma. Despite radiation therapy, the patient died about a year later.

*Comment:* Not only adenocarcinoma but also

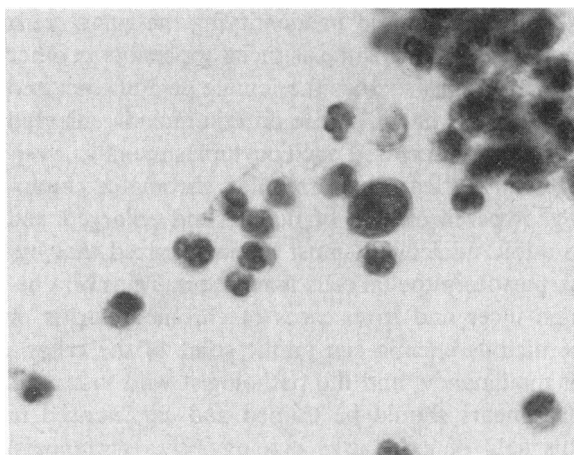


Figure 3.—(Case 3) Reticulum-cell sarcoma  $\times 1,000$ .

malignant lymphoma of the stomach may be detected cytologically. The differentiation of adenocarcinoma and reticulum-cell sarcoma by cytologic examination of gastric aspirates is difficult. Although the malignant cells in this case were detected cytologically, they were not specifically identified as being from a reticulum-cell sarcoma. (Three other cases of malignant lymphoma were included in the present series, and in two of them the cytologic smear was called positive and the lesion identified as lymphoma. One case was not diagnosed cytologically, and hence is included among the false negative cases.)

## Discussion

The degree of accuracy attained in this series, and that reported by other investigators provides reasonable assurance that if the result of a properly executed gastric cytologic examination is negative, gastric malignant disease is unlikely. Obviously, in all reported series some false negatives occur, and gastric cytology should not be the sole technique used to exclude the diagnosis of gastric cancer. An unequivocal positive report (Class V), however, is highly significant and should be considered as a definitive diagnosis of cancer.

In order to achieve satisfactory results, attention to detail is essential. The specimen should be obtained only by specially trained cytotechnologists or nurses. Random gastric aspirations obtained by untrained personnel and sent routinely to the laboratory are usually unsatisfactory. Speed in the preparation and fixation of the smears, with immediate chilling of the aspirate, is absolutely essential to prevent cellular degeneration.

The criteria used in identifying malignant cells are essentially the same as those applicable in other anatomic sites such as the female genital tract and respiratory system. These criteria include enlarged nuclei with increased nucleocytoplasmic ratio, variation in nuclear size, irregular chromatin clumping, hyperchromasia of nuclei, and enlarged and multiple nucleoli. It must be emphasized that hyperplastic epithelial cells from the margins of a benign ulcer and from cases of chronic gastritis or pernicious anemia can mimic some of the criteria of malignancy, and the pathologist who interprets the smears should be trained and experienced in this field of exfoliative cytology. If a pathologist interested and trained in this area of cytopathology is available, results comparable with those reported from large centers may be achieved in smaller hospitals with a relatively small number of cases.

Since gastric exfoliative cytology, unlike vaginal cytology, is time-consuming and expensive, it is not suitable as a routine screening procedure for all patients in the cancer age group. However, it should be done in any case in which a patient of "cancer age" has gastrointestinal symptoms suggestive of gastric cancer, or has any significant gastric abnormality on x-ray or gastroscopic examination or any other abnormalities arousing suspicion of cancer. It is also useful in the post-gastrectomy follow-up of patients with known gastric cancer, since recurrences are often easily detected.<sup>11</sup> Finally, it may be worth while to carry out periodic screening of certain specific groups at high risk of gastric carcinoma, such as patients with pernicious anemia<sup>2,6</sup> (we have had no specific experience with this latter category of patients).

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